Is the interruption of antiretroviral treatment during pregnancy an additional major risk factor for mother-to-child transmission of HIV

Is the Interruption of Antiretroviral Treatment During Pregnancy an Additional Major Risk Factor for Mother-to-Child Transmission of HIV Type 1?

Luisa Galli,[1] Donella Puliti,[2] Elena Chiappini,[1] Clara Gabiano,[3] Gabriele Ferraris,[4] Federica Mignone,[3] Alessandra Viganò,[5] Carlo Giaquinto,[7] Orazio Genovese,[8] Gianfranco Anzidei,[9] Raffaele Badolato,[11] Wilma Buffolano,[12] Anna Maccabruni,[13] Filippo Salvini,[6] Monica Cellini,[14] Maurizio Ruggeri,[15] Mariano Manzionna,[16] Stefania Bernardi,[10] Pierangelo Tovo,[3] and Maurizio de Martino,[1] for the Italian Register for HIV Infection in Children[a]

[1]Department of Pediatrics, University of Florence, and [2]Clinical and Descriptive Epidemiology Unit, Centre for the Study and Prevention of Tumours, Research Institute of the Tuscany Region, Florence, [3]Department of Pediatrics, University of Turin, Turin, [4]Division of Neonatology, Mangiagalli Hospital, [5]Division of Pediatrics, University of Milan, Sacco Hospital, and [6]Division of Pediatrics, University of Milan, S. Paolo Hospital, Milan, [7]Department of Pediatrics, University of Padua, Padua, [8]Department of Pediatrics, Gemelli Hospital, [9]Division of Pediatrics, Spallanzani Hospital, and [10]AIDS Unit, Department of Pediatrics, Bambino Gesù Children's Hospital, Rome, [11]Department of Pediatrics, University of Brescia, Brescia, [12]Department of Pediatrics, Federico II University, Naples, [13]Department of Infectious Disease, University of Pavia, Pavia, [14]Department of Mother and Child, University of Modena, Modena, [15]Division of Pediatrics, Hospital of Bergamo, Bergamo, and [16]Neonatology Unit, Department of Pediatrics, University of Bari, Bari, Italy

Background. There is currently an experts' agreement discouraging interruption of antiretroviral treatment (ART) during the first trimester of pregnancy in women infected with human immunodeficiency virus type 1 (HIV-1). However, this recommendation is poorly supported by data. We evaluated the effects of discontinuing ART during pregnancy on the rate of mother-to-child transmission.

Methods. Logistic regression models were performed in a prospective cohort of 937 children who were perinatally exposed to HIV-1 to estimate adjusted odds ratios for confounding factors on mother-to-child transmission, including maternal interruption of ART.

Results. Among 937 pregnant women infected with HIV-1, ART was interrupted in 81 (8.6%) in the first trimester and in 11 (1.2%) in the third trimester. In the first trimester, the median time at suspension of ART was 6 weeks (interquartile range [IQR], 5–6 weeks) and the time without treatment was 8 weeks (IQR, 7–11 weeks). In the third trimester, the median time at suspension of ART was 32 weeks (IQR, 23–36 weeks) and the time without treatment was 6 weeks (IQR, 2–9 weeks). The plasma viral load was similar in women who had treatment interrupted in the first trimester and in those who did not have treatment interrupted.

Overall, the rate of mother-to-child transmission in the whole cohort was 1.3% (95% confidence interval [CI], 0.7%–2.3%), whereas it was 4.9% (95% CI, 1.9%–13.2%) when ART was interrupted in the first trimester and 18.2% (95% CI, 4.5%–72.7%) when ART was interrupted in the third trimester. In the multiple logistic regression models, only interruption of ART during either the first or the third trimester, maternal mono- or double therapy, delivery by a mode other than elective cesarean delivery, and a viral load at delivery >4.78 $\log_{10}$ copies/mL were independently associated with an increased rate of mother-to-child transmission.

Conclusions. Discontinuing ART during pregnancy increases the rate of mother-to-child transmission of HIV-1, either when ART is stopped in the first trimester and subsequently restarted or when it is interrupted in the third trimester. This finding supports recommendations to continue ART in pregnant women who are already receiving treatment for their health.

After the results of the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group [1], several prospective studies have confirmed the effectiveness of antiretroviral treatment (ART) during pregnancy in decreasing the rate of mother-to-child transmission

Received 13 August 2008; accepted 9 December 2008; electronically published 23 March 2009.

Clinical Infectious Diseases 2009; 48:1310–7

1058-4838/2009/4809-0026$15.00
DOI: 10.1086/597774

Reprints or correspondence: Prof. Maurizio de Martino, Dept. of Pediatrics, University of Florence, Via Luca Giordano, 13, Florence I-50132, Italy (maurizio.demartino@unifi.it).

[a] Members of the Italian Register of HIV Infection in Children are listed at the end of the text.

(MTCT) of HIV-1 [2–5]. In developed countries, the synergic effect of ART in the mother and newborn, cesarean delivery, and avoidance of breast-feeding have resulted in a rate of MTCT of <2% [2–5]. In the HAART era, the rate of MTCT is ~1%, probably because of the strong effect of HAART on the maternal viral load [6]. Therefore, there is a consensus on the benefits of HAART for the mother's health and for prevention of MTCT, provided that drugs with a potential toxicity for the offspring are avoided [7]. Data from prospective registries [8] support lack of teratogenicity with exposure to antiretroviral drugs during pregnancy, but with the increasing use of new molecules, monitoring of birth defects is continually needed. An increasing number of treated women are now identified as pregnant, and presently there is an experts' opinion discouraging a temporary discontinuation of ART during the first trimester [7]. However, this opinion is only partially supported by evidence. To date, insufficient data support an increase in the rate of MTCT as a consequence of ART discontinuation during pregnancy. We performed an analysis involving a large cohort of children prospectively enrolled in the Italian Register for HIV Infection in Children, to evaluate the effect of discontinuation of ART during pregnancy on the rate of MTCT.

METHODS

Data collection. The Italian Register for HIV Infection in Children is a nationwide multicenter study of children perinatally exposed to HIV-1 that was instituted in 1985. Data come from a network of 106 participating pediatric centers located throughout Italy, representing the overall population of exposed infants in Italy [3]. Informed consent at the local pediatric center and National Privacy Agency permission are obtained. Both at-risk children identified at birth and infected children identified after birth are enrolled. In this study, only exposed children identified at birth who were born to treated mothers and who had known infectious status were considered [3]. Data with regard to mother-infant pairs were collected as described elsewhere [3, 9]. Detailed data on the type of regimen(s), gestational age at beginning and end of ART (for each single regimen if switches occurred during pregnancy), and ART administered intrapartum and/or to the newborn were included. Maternal data were obtained at each pediatric center from an infectious diseases report and/or a gynecologist's report, and they were recorded at the infant's first examination, at birth. From 2001, information on the maternal plasma viral RNA load and $CD4^+$ cell counts at the time of delivery and information on the last antiretroviral regimen (the type and the date of initiation) prior to pregnancy were collected. Because this information was uniformly available only since 2002, only children born in 2002 or later were evaluated in the present study. Viral loads and $CD4^+$ cell counts were evaluated as described elsewhere [3, 9]. Both baseline and follow-up information on the infant's infection status, HIV-1 antibodies, and viral markers (HIV-1 DNA or RNA detection) were collected [3].

Case definition. Infection in children [3, 9, 10], elective cesarean delivery [2], and duration of ART during pregnancy [9] were defined as reported. To evaluate the effect of type of ART on the rate of MTCT, we defined monotherapy as zidovudine (according to the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group protocol), double therapy as any regimen including 2 nucleoside reverse-transcriptase inhibitors (NRTI), and HAART as any combination regimen with ⩾3 antiretroviral drugs (no mother received a triple NRTI regimen). Among HAART regimens, a nevirapine-based regimen was defined as any triple regimen including 2 NRTIs plus nevirapine, and a protease inhibitor (PI)–based regimen was defined as any triple (or more) regimen including NRTIs plus a PI. When >1 regimen was received during pregnancy, the more complex (i.e., HAART vs. double) was considered. Maternal interruption of ART was defined as the discontinuation of any ART for >15 days. Shorter periods of interruption, in fact, could not be reported by the mothers. Moreover, it is usually believed that plasma viral RNA load significantly decreases after 2 weeks of treatment, and perinatal guidelines recommend monitoring maternal viral load 2–6 weeks after initiating or changing ART [7]. The gestational age at ART initiation was defined as the week at the beginning of the first ART regimen for women who did not receive therapy during the periconceptional period.

Statistical analysis. Analyses were performed on data reported through December 2005 for children followed up since birth who were born from 1 January 2002 through 31 December 2004. Children born from 1 January 2005 through 30 June 2005 were excluded from analysis because of the large percentage of exposed children with an undetermined HIV-1 status.

Data were expressed as median and interquartile range (IQR) or as mean and 95% CI. Differences in proportions were evaluated by the χ^2 test. A nonparametric 3-sample test was performed to test the hypothesis of median equality. The analysis of variance was used to test for differences in maternal viral load at delivery. To evaluate the association of ART interruption with the rate of MTCT, logistic regression models were performed to estimate adjusted ORs for factors potentially influencing the rate of MTCT: infant's sex, gestational age (<37 weeks, ⩾37 weeks, or unknown), plasma viral RNA load at delivery (<2.6, 2.6–4.00, 4.01–5.78, >5.78 $\log_{10}$ copies/mL, or unknown), $CD4^+$ cell count at delivery (<200, 200–499, ⩾500 cells/μL, or unknown), mode of delivery (vaginal delivery, elective cesarean delivery, cesarean delivery other than elective, or unknown), maternal ART in pregnancy (zidovudine monotherapy, double therapy, HAART, or unknown), maternal interruption of ART (yes or no), intrapartum ART (yes, no, or unknown), and neonatal ART (yes, no, or unknown). Because

no child was breast-fed, the mode of feeding was not included in the regression analyses. To better evaluate interaction between quantitative variables potentially associated with the rate of MTCT, an additional logistic regression model with $\log_{10}$ plasma viral RNA load and $\log_{10}$ $CD4^+$ cell count as continuous variables was performed for a subgroup of mother-child pairs with both variables known.

RESULTS

Mother-infant pairs. Overall, 937 of 1016 mother-child pairs receiving ART entered the study; 79 (7.8%) of the exposed infants were excluded because they were lost to follow-up before ascertainment of infectious status. The characteristics of the 937 mothers and children are shown in table 1. Intrapartum and neonatal prophylaxis consisted of zidovudine in all but 8 cases in which nevirapine was given. Maternal plasma viral load was known in 630 (67.2%) of the 937 mother-child pairs. Of the 630 women with known viral load, the majority (453 [71.9%]) showed an undetectable plasma viral load (tested by an assay with a cutoff value of 50 copies/mL [$n = 340$] and 400 copies/mL [$n = 113$]). Characteristics of mother-child pairs were compared according to known or unknown maternal plasma viral load. Frequency of intrapartum ART administration was higher when maternal viral load was known (586 [93.0%] of 630 women vs. 261 [85.0%] of 307 women; $\chi^2 = 15.21.5$; $P < .001$), and frequency of prepartum HAART administration was higher when maternal viral load was known (454 [72.1%] of 630 women vs. 197 [64.2%] of 307 women; $\chi^2 = 6.07$; $P = .014$); no difference was observed in the frequency of mode of elective cesarean delivery (580 [92.1%] of 630 women vs. 280 [91.2%] of 307 women; $\chi^2 = 0.20$; $P = .653$), the use of neonatal ART (614 [97.5%] of 630 infants vs. 301 [98.0%] of 307 infants; $\chi^2 = 0.31$; $P = .579$), and the infant's infectious status (8 [1.3%] of 630 cases vs. 4 [1.3%] of 307 cases; $\chi^2 = 0.002$; $P = .966$). The maternal viral load decreased as the complexity of the ART regimen increased. The mean plasma viral load was 2.6 $\log_{10}$ copies/mL (95% CI, 2.2–2.9 $\log_{10}$ copies/mL), 2.4 $\log_{10}$ copies/mL (95% CI, 2.2–2.6 $\log_{10}$ copies/mL), and 1.9 $\log_{10}$ copies/mL (95% CI, 1.8–2.0 $\log_{10}$ copies/mL) in women receiving monotherapy, double therapy, or HAART, respectively (analysis of variance, $F = 17.2$; $P < .001$). The median gestational age at the beginning of treatment was 18 weeks (IQR, 13–35 weeks), 18 weeks (IQR, 13–25 weeks), and 13 weeks (IQR, 6–22 weeks) in women receiving monotherapy, double therapy, or HAART, respectively, thus decreasing with the increase in the ART complexity ($\chi^2 = 36.8$; $P < .001$). The proportion of women with detectable viral load did not differ according to trimester at start of ART when monotherapy was given ($n = 50$; 78.6% during the first trimester, 55.0% during the second trimester, and 56.3% during the third trimester; $\chi^2 = 2.27$; $P = .321$) In addition, the pro-

Table 1. Characteristics of 937 mother-child pairs in our study of mother-to-child transmission of HIV-1 infection.

Variable	No. (%) of mother-child pairs
Mother	
Type of ART	
Monotherapy	99 (10.6)
Double therapy	187 (20.0)
HAART	651 (69.5)
Type of ART before interruption ($n = 81$)	
Nevirapine-based HAART	27 (33.3)
Protease inhibitor-based HAART	27 (33.3)
Other regimen of HAART	19 (23.5)
Nonspecified HAART	2 (2.5)
Double therapy	3 (3.7)
Monotherapy	3 (3.7)
Type of ART after interruption ($n = 81$)	
Nevirapine-based HAART	33 (40.7)
Protease inhibitor–based HAART	33 (40.7)
Other regimen of HAART	6 (7.4)
Nonspecified HAART	2 (2.5)
Double therapy	3 (3.7)
Monotherapy	4 (4.9)
Type of delivery	
Elective cesarean	860 (91.8)
Cesarean other than elective	51 (5.4)
Vaginal	20 (2.1)
Unknown	6 (0.6)
Viral load at delivery, $\log^{10}$ copies/mL	
<2.6	453 (48.3)
2.6–4.00	133 (14.2)
4.01–4.78	C36 (3.8)
>4.78	8 (0.9)
Unknown	307 (32.8)
$CD4^+$ cell count at delivery, cells/μL	
<200	43 (4.6)
200–499	267 (28.5)
⩾500	265 (28.3)
Unknown	362 (38.6)
Intrapartum ART	
Yes	847 (90.4)
No	90 (9.6)
Child	
Sex	
Male	482 (51.4)
Female	455 (48.6)
Gestational age	
<37 weeks	187 (20.0)
⩾37 weeks	745 (79.5)
Unknown	5 (0.5)
Neonatal ART	
Yes	915 (97.7)
No	22 (2.3)
Infectious status	
Infected	12 (1.3)
Uninfected	925 (98.7)

NOTE. HAART was defined as ⩾3 antiretroviral drugs. ART, antiretroviral therapy.

Table 2. Characteristics of the 12 mother-child pairs in which the infants were infected.

Identifier	Maternal ART regimen			Interruption of ART		Maternal HIV-1 RNA load at delivery, copies/mL	$CD4^+$ cell count at delivery, cells/μL	Gestational age, weeks	Intrapartum ART	Neonatal ART
	At beginning of pregnancy	After interruption	After switching without interruption	During first trimester	During third trimester					
1	ddI+TDF+T20	ddI+TDF+NFV	…	Yes	No	28,110	74	33	Yes	Yes
2	ddI+d4T+LPV/RIT	…	AZT	No	No	Unknown	Unknown	Unknown	Yes	Yes
3	AZT+3TC+NVP	AZT+3TC+NVP	…	Yes	No	780	781	38	Yes	Yes
4	AZT+3TC+NFV	…	…	No	No	1710	839	38	Yes	Yes
5	AZT	…	…	No	No	Unknown	Unknown	31	No	Yes
6	d4T+TDF+LPV/RIT	AZT+3TC+NVP	…	Yes	No	<50	326	27	No	Yes
7	d4T+3TC+NFV	d4T+3TC+NFV	…	No	Yes	600,000	410	31	Yes	Yes
8	AZT+ 3TC	AZT + 3TC	…	Yes	No	500,000	200	37	Yes	No
9	AZT+3TC+NVP	…	…	No	No	16,900	468	39	Yes	Yes
10	AZT+3TC	…	…	No	No	54	390	38	Yes	Yes
11	AZT+3TC+NVP	AZT+3TC+NVP	…	No	Yes	Unknown	Unknown	21	Yes	Yes
12	AZT	…	…	No	No	2800	141		Yes	Yes

NOTE. All deliveries were elective cesarean deliveries. AZT, zidovudine; ddI, didanosine; d4T, stavudine; LPV/RIT, lopinavir-ritonavir; NFV, nelfinavir; NVP, nevirapine; TDF, tenofovir; T20, enfuvirtide; 3TC, lamivudine.

portion of women with detectable viral load did not differ according to the trimester during which ART was initiated when double therapy was given ($n = 126$; 38.1% during the first trimester, 37.3% during the second trimester, and 47.1% during the third trimester; $\chi^2 = 0.56$; $P = .756$). However, the proportion of women with detectable viral load was significantly higher when HAART (given to 454 women) was started during the third trimester (45.9%), compared with during the second (17.5%) or first trimester (17.8%; $\chi^2 = 25.81$; $P < .001$). Women treated with HAART who had a known plasma viral load had similar mean plasma viral loads when 281 women who were treated with a PI-based regimen (1.95 $\log_{10}$ copies/mL; 95% CI, 1.77–2.07 $\log_{10}$ copies/mL) were compared with 328 women treated with a nevirapine-based regimen (1.85 $\log_{10}$ copies/mL; 95% CI, 1.65–1.92 $\log_{10}$ copies/mL; Student's t test, 1.29; $P = .197$).

Discontinuation and subsequent restart of ART was reported in 81 (8.6%) of the 937 mother-child pairs in the first trimester of pregnancy (median time at suspension, 6 weeks [IQR, 5–6 weeks]; median time without treatment, 8 weeks [IQR, 7–11 weeks]) and in 11 (1.2%) of the mother-child pairs in the third trimester (median time at suspension, 32 weeks [IQR, 23–36 weeks]; median time without treatment, 6 weeks [IQR, 2–9 weeks]). Only 1 mother, who gave birth to an uninfected child, had treatment interrupted during both the first and the third trimesters. ART was more frequently interrupted at the beginning of pregnancy in women treated with HAART (74 [11.4%] of 651 women) than in women treated with double therapy (3 [1.6%] of 187 women) or with monotherapy (4 [4.0%] of 99 women; χ^2 test, 20.50; $P < .001$).

We checked whether women switched therapy after interruption to a less or more active regimen, but the proportions of women treated with a nevirapine- or PI-based HAART regimen before or after treatment interruption were similar (table 1). Treatment was restarted with the same class of antiretroviral drugs in 47 (58.0%) of the 81 women, among whom 19 (23.5%) received the same nevirapine-based regimen that they received prior to the interruption.

Among women whose viral load at delivery was known, the mean plasma viral load was similar in those who had treatment interrupted in the first trimester (2.04 $\log_{10}$ copies/mL; 95% CI, 1.81–2.26 $\log_{10}$ copies/mL) and in those who did not have treatment interrupted (2.04 $\log_{10}$ copies/mL; 95% CI, 1.95–2.14 $\log_{10}$ copies/mL; Student's t test, −0.04; $P = .967$). Similarly, the mean $CD4^+$ cell count at delivery was similar in women who had treatment interrupted (2.63 $\log_{10}$ cells/μL; 95% CI, 2.57–2.69 $\log_{10}$ cells/μL) and in those who did not have treatment interrupted (2.65 $\log_{10}$ cells/μL; 95% CI, 2.65–2.67 $\log_{10}$ cells/μL; Student's t test, −0.40; $P = .689$). Among HAART-treated women who had therapy interrupted and who had known plasma viral load, we found no difference in mean plasma viral load between 29 women treated with a PI-based regimen (2.06 $\log_{10}$ copies/mL; 95% CI, 1.70–2.42 $\log_{10}$ copies/mL) and 28 women treated with a nevirapine-based regimen (1.85 $\log_{10}$ copies/mL; 95% CI, 1.69–2.01 $\log_{10}$ copies/mL; Student's t test, 1.12; $P = .268$).

MTCT rate and confounding factors. Overall, the rate of MTCT in the whole cohort was 1.3% (95% CI, 0.7%–2.3%). The rate of MTCT among children born to mothers who had ART interrupted in the first trimester was 4.9% (95% CI, 1.9%–13.2%), and the rate of MTCT among children born to mothers who had ART interrupted in the third trimester was 18.2% (95% CI, 4.5%–72.7%). Characteristics of the 12 mother-child pairs in which the children were infected are shown in table 2.

To evaluate the role of different risk factors for MTCT, univariate and multiple logistic regression models were performed. Maternal monotherapy or double therapy, interruption of ART during either the first or the third trimester, delivery by a mode other than elective cesarean delivery, and a viral load at delivery >4.78 $\log_{10}$ copies/mL were associated with an increased rate of MTCT (table 3). Plasma viral load >4.78 $\log_{10}$ copies/mL was associated with a 30-fold increased risk of transmission. Other factors (maternal $CD4^+$ cell count at delivery, trimester at the start of ART, child's sex, and intrapartum and neonatal ART) were not significantly associated with the rate of MTCT.

When we included in an additional model the 79 exposed infants lost to follow-up, with the assumption that all these children were uninfected, results were unchanged (adjusted OR for treatment interruption in the first trimester, 11.4; in the third trimester, 34.1). The probability of infection in children

Table 3. Univariate and logistic regression analysis of risk factors for mother-to-child transmission of HIV-1 infection.

Factor	No. of infected infants/total no. of infants	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Type of maternal ART					
Monotherapy	5/99	Reference		Reference	
Double	1/187	0.10 (0.01–0.88)	.038	0.21 (0.02–2.21)	.192
HAART	6/651	0.18 (0.05–0.58)	.005	0.17 (0.04–0.80)	.025
Trimester at start of ART					
First	5/463	Reference		Reference	
Second	4/321	1.16 (0.31–4.34)	.830	0.54 (0.10–3.06)	.487
Third	3/149	1.88 (0.44–7.97)	.391	0.92 (0.15–5.51)	.929
Unknown	0/4	NA		NA	
Interruption of ART					
During the first trimester					
No	8/856	Reference		Reference	
Yes	4/81	5.51 (1.62–18.70)	.006	10.33 (2.02–52.91)	.005
During the third trimester					
No	10/926	Reference		Reference	
Yes	2/11	20.36 (3.89–106.42)	<.001	46.86 (4.28–512.64)	.002
Type of delivery					
Elective cesarean	10/860	Reference		Reference	
Cesarean other than elective	2/51	3.47 (0.74–16.27)	.115	5.9 (0.93–37.28)	.059
Vaginal	0/20	NA		NA	
Unknown	0/6	NA		NA	
Viral load at delivery, $\log_{10}$ copies/mL					
<2.6	2/453	Reference		Reference	
2.61–4.00	3/133	5.20 (0.86–31.48)	.073	4.78 (0.65–34.98)	.124
4.01–4.78	1/36	6.44 (0.57–72.82)	.132	7.41 (0.52–105.87)	.140
>4.78	2/8	75.17 (9.03–625.60)	<.001	29.19 (1.80–473.81)	.018
Unknown	4/307	2.98 (0.54–16.35)	.210	7.69 (0.64–92.97)	.109
$CD4^+$ cell count at delivery, cells/μL					
<200	1/43	Reference		Reference	
200–499	5/267	0.80 (0.09–7.03)	.842	0.99 (0.09–11.09)	.994
⩾500	2/265	0.32 (0.03–3.60)	.356	0.88 (0.06–12.59)	.923
Unknown	4/362	0.47 (0.05–4.30)	.503	0.25 (0.01–4.44)	.341
Sex of child					
Female	5/455	Reference		Reference	
Male	7/482	1.33 (0.42–4.21)	.632	1.02 (0.25–4.13)	.983
Intrapartum ART					
No	2/90	Reference		Reference	
Yes	10/847	0.53 (0.11–2.44)	.411	0.53 (0.09–3.11)	.481
Neonatal ART					
No	1/22	Reference		Reference	
Yes	11/915	0.26 (0.03–2.07)	.201	0.84 (0.04–18.30)	.912

NOTE. HAART was defined as ⩾3 antiretroviral drugs. ART, antiretroviral treatment; NA, not applicable.

in this group was very low, because missing infected children are regained by periodical cross-matches with the Italian National AIDS Registry, to which all AIDS cases must be reported [11].

To check the interference of missing values for maternal plasma viral load, 3 logistic regression models were performed. Interruption of ART in the first trimester was associated with an adjusted OR of 10.33 (95% CI, 2.02–52.91; $P = .005$), and interruption of ART in the third trimester was associated with an adjusted OR of 46.86 (95% CI, 4.28–512.64; $P = .002$) in the whole cohort, with the inclusion of maternal viral load as a category with missing values. When only cases with known maternal viral load were included, the adjusted OR for interruption of ART in the first trimester was 11.45 (95% CI, 1.58–83.08; $P = .016$) and in the third trimester was 24.33 (95% CI, 0.77–765.92; $P = .070$). When maternal viral load was excluded, the adjusted OR for interruption of ART in the first trimester was 8.32 (95% CI, 1.88–36.90; $P = .005$) and in the third trimester was 40.52 (95% CI, 4.24–387.64; $P = .001$) in the whole cohort.

Finally, a logistic regression model on a subgroup ($n = 538$) of mother-child pairs with both known plasma viral load and known $CD4^+$ cell count was performed, including these factors as continuous variables. Treatment interruption in the first trimester was associated with an adjusted OR of 10.70 (95% CI, 1.48–77.18), and treatment interruption in the third trimester was associated with an adjusted OR of 30.38 (95% CI, 0.98–941.66). Plasma viral load was associated with an adjusted OR of 2.50 (95% CI, 1.27–4.91), and $CD4^+$ cell count was associated with an adjusted OR of 1.87 (95% CI, 0.07–53.26). Thus, treatment interruption in the first trimester was associated with a 10-fold increased risk of MTCT, whereas a plasma viral load increase of 1 $\log_{10}$ copies/mL doubled the risk of MTCT.

DISCUSSION

To our knowledge, this is the first study to reveal that discontinuing ART during pregnancy increases the rate of MTCT of HIV-1, either when ART is stopped in the first trimester and subsequently restarted, or when it is interrupted in the third trimester. The last finding was partly expected, because discontinuation of treatment could lead to a viremic rebound [12, 13] and because a higher viral load near the time of delivery increases the risk of MTCT, as we and others have clearly shown [14, 15]. The incremental risk of MTCT associated with treatment interruption is high among all treated women, even among HAART-treated women, maybe because the viremic rebound is stronger if the virological potency of therapy is higher. Therefore, our findings confirm the recommendation that pregnant women infected with HIV-1 who receive ART should continue treatment after the first trimester, particularly at the end of pregnancy [7]. More interestingly, we found that interruption of ART early in pregnancy increased the rate of MTCT both in the whole cohort and among children born to HAART-treated women. To our knowledge, no other large study has investigated this issue. Of note, in our cohort, temporary ART discontinuation early in pregnancy is more frequent in women receiving HAART, probably because of the fear of drug toxicity in the embryo. However, temporary discontinuation led to a 10-fold increase in the rate of MTCT, overcoming all other risk factors, except for the independent factor of high plasma viral RNA load at delivery. When viral load increased by 1 $\log_{10}$ copies/mL, the risk of MTCT was, indeed, more than doubled. A small proportion of HAART-treated women may have high plasma viral loads because of poor compliance or mutations associated with viral resistance [16]. Nevertheless, we found no difference in predelivery plasma viral load between mothers who temporarily discontinued therapy and mothers who did not. It might be speculated that a transient viral load increase, occurring close to the time of ART interruption, favors HIV-1 transmission.

We also investigated whether a lower antiretroviral potency of the regimen administered after suspension could lead to higher risk of MTCT, but the proportions of nevirapine-based or PI-based regimens were similar before and after interruption. However, it is possible that virological failure occurred more frequently because of nevirapine-resistance mutations [17] in those women who discontinued and restarted the same nevirapine-based regimen. Viral load at delivery was similar in the women treated with a PI-based regimen and in those treated with a nonnucleoside reverse-transcriptase inhibitor–based regimen in both the whole cohort and in those who had therapy interrupted. In addition, we found a trend toward higher viral loads in women treated with a PI-based regimen than in those treated with an nonnucleoside reverse-transcriptase inhibitor–based regimen, as recently was reported by the European Collaborative Study [18]. It is possible that women with lower baseline viral loads (before or at the beginning of pregnancy) are more often treated with nonnucleoside reverse-transcriptase inhibitor–based regimens, or the pharmacokinetic peculiarities of ART in pregnancy may be involved [18].

Because our data are from a large pediatric cohort, a limitation in our analyses is that some detailed information on the mothers was lacking. First of all, maternal viral load at delivery was unknown for ~30% of mother-child pairs. However, when mother-child pairs were compared according to whether maternal viral load was known or unknown, exactly the same MTCT rate was found. As an additional check, 3 different logistic regression models were performed, but the main role of ART interruption in pregnancy was constantly confirmed. Another critical point is the unavailability in our database of information on the reasons for ART discontinuation during

pregnancy. Therapy could be discontinued for several reasons: the development of virological failure or resistance mutations, the occurrence of adverse effects, or the desire to avoid fetal exposure during the first trimester. On the other hand, ART interruption was not homogeneously distributed during the whole pregnancy, peaking at 6 and 32 weeks. We think that avoidance of fetal exposure during the first trimester and intolerance of treatment are the most probable reasons for ART discontinuation, and if so, it would be unlikely that women who had ART suspended were a priori at higher risk of MTCT because of virological failure or resistance mutations. Unfortunately, we had no data on maternal viral load during gestation. Moreover, we could not assess whether infected children born to mothers who had ART interrupted acquired the infection in utero or perinatally [19], because we do not systematically measure HIV-1 RNA or DNA load during the first 24–48 h of life.

We investigated all interactions between variables that we thought were biologically convincing. Other important factors might be compliance to ART and genotype resistance in the mothers, but these data were lacking in our database. Finally, the very low number of infected children in the whole cohort and, consequently, the wide 95% CIs found, are additional caveats. Additional studies, prospectively performed using large cohorts of mother-child pairs starting from the beginning of gestation, may confirm our findings. It may be surprising that we found no relationship between intrapartum and neonatal therapy and the rate of MTCT, but the numbers of mother-child pairs who were not receiving intrapartum and neonatal prophylaxis were too small to draw any conclusion. Moreover, we found no differences according to trimester at start of ART, even if a higher proportion of HAART-treated women had a detectable viral load at delivery when treatment was used during the third trimester, compared with the first or second trimester. This finding supports recently revised guidelines [7] that recommend that, in women who do not require ART for their own health, ART for MTCT prophylaxis may be started during the second trimester, preferably with a 3-drug regimen.

The main finding of our study is that no other factors but the discontinuation of ART and high maternal viral load at delivery are associated with an increased risk of MTCT. Thus, although concerns about potential toxicity in the fetus need to be completely clarified, counseling on the temporary discontinuation of ART in the first trimester should consider both the need for maternal health [7] and the increased risk of HIV-1 transmission to the offspring. We believe that our findings may be useful for physicians who care for women infected with HIV-1 and for specialists who determine guidelines.

OTHER PARTICIPANTS OF THE ITALIAN REGISTER FOR HIV INFECTION IN CHILDREN

F. De Benedictis and P. Osimani (Ancona); D. La Rovere and M. Quercia (Bari); M. Ruggeri (Bergamo); F. Baldi, M. Ciccia, A. Faldella, and M. Masi (Bologna); A. Plebani and E. Spinelli (Brescia); M. Dedoni and D. Gariel (Cagliari); P. Chiarello and M. G. Magnolia (Catanzaro); M. Sticca (Como); L. Vivalda (Cuneo); T. Bezzi and E. Fiumana (Ferrara); L. Bianchi, N. Battiglia, and P. Gervaso (Florence); E. Bondi, D. Cosso, C. Gotta, L. Ginocchio, R. Rosso, and C. Viscoli (Genoa); C. Amoretti (Imperia); S. Esposito, F. Farina, V. Giacomet, R. Lipreri, A. Plebani, E. Salvatici, and S. Stucchi (Milan); G. Palazzi and P. Paolucci (Modena); G. De Luca, A. Giannattasio, F. Tancredi, and L. Tarallo (Naples); O. Rampon (Padua); E. Dalle Nogare, A. Romano, and M. Saitta (Palermo); B. Mariani (Pavia); P. Biver, R. Consolini, and G. Palla (Pisa); A. De Fanti, I. Dodi, and M. Verna (Parma); G. Bove, A. M. Casadei, G. Castelli Gattinara, S. Catania, A. M. Martino, and M. M. Sirufo (Rome); A. Ganau (Sassari); L. Cristiano (Taranto); C. Scolfaro and A. Versace (Turin); V. Portelli (Trapani); L. Gentilini and A. Mazza (Trento); M. Bernardon, J. Bua, and M. Rabusin (Trieste); A. Pellegatta (Varese); and P. Fortunati (Verona).

Acknowledgments

We thank Dr. Patrizio Pezzotti for his helpful statistical suggestions.

Financial support. The Italian Ministero della Sanità, Istituto Superiore di Sanità, VI Programma Nazionale Ricerca sull'AIDS 2006, Epidemiologia HIV/AIDS (Grant 20G.13).

Potential conflicts of interest. C. Giaquinto has been a consultant to GlaxoSmithKline, Abbott, Bristol-Myers Squibb, Tibotec, Boehringer-Ingelheim, Gilead Sciences, Pfizer, Sanofi Pasteur, and GSK-Bio, and has received research grants from GlaxoSmithKline, Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, and Sanofi Pasteur. All other authors: no conflicts.

References

1. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med **1994**; 331:1173–80.
2. The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1: a meta-analysis of 15 prospective cohort studies. N Engl J Med **1999**; 340:977–87.
3. The Italian Register for Human Immunodeficiency Virus Infection in Children. Determinants of mother-to-infant human immunodeficiency virus 1 transmission before and after the introduction of zidovudine prophylaxis. Arch Pediatr Adolesc Med; **2002**; 156:915–21.
4. Mandelbrot L, Landreau A, Rekacevicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. JAMA **2001**; 285:2083–93.
5. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. J Acquir Immune Defic Syndr **2002**; 29:484–94.
6. European Collaborative Study. Mother-to-child transmission of HIV

infection in the era of highly active antiretroviral therapy. Clin Infect Dis **2005**; 40:458–65.
7. Perinatal HIV Guidelines Working Group. Public health service task force recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 8 July **2008**:1–98. Available at: http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf. Accessed 9 March 2009.
8. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 July 2005. Wilmington, NC: Registry Coordinating Center, **2005**. Available at: http://www.APRegistry.com. Accessed 9 March 2009.
9. Galli L, Puliti D, Chiappini E, et al.; the Italian Register for HIV Infection in Children. Lower mother-to-child HIV-1 transmission in boys is independent of type of delivery and antiretroviral prophylaxis. J Acquir Immune Defic Syndr **2005**; 40:479–85.
10. Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. **1994**. Available at: http://www.cdc/mmwr/preview/mmwrhtml/00032890.htm. Accessed March 20, 2009.
11. de Martino M, Tovo PA, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. JAMA **2000**; 284:190–7.
12. Bucceri AM, Somigliana E, Matrone R, et al. Discontinuing combination antiretroviral therapy during the first trimester of pregnancy: insights from plasma human immunodeficiency virus–1 RNA viral load and CD4 cell count. Am J Obstet Gynecol **2003**; 189:545–51.
13. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. $CD4^+$ count–guided interruption of antiretroviral treatment. N Engl J Med **2006**; 355:2283–96.
14. Garcia PM, Kalish LA, Pitt J, et al.; the Women and Infants Transmission Study Group. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. New Engl J Med **1999**; 341:394–402.
15. European Collaborative Study. Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. AIDS **1999**; 13:1377–85.
16. Duran AS, Losso MH, Salomon H, et al. Drug resistance among HIV-infected pregnant women receiving antiretrovirals for prophylaxis. AIDS **2007**; 21:199–205.
17. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. N Engl J Med **2007**; 356:135–47.
18. European Collaborative Study. Time to undetectable viral load after highly active antiretroviral therapy initiation among HIV-infected pregnant women. Clin Infect Dis **2007**; 44:1647–56.
19. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intrauterine and intrapartum transmission. AIDS **1995**; 9:F7–11.